

# **A model-based evaluation of the long-term cost-effectiveness of systematic case-finding for COPD in primary care**

Tosin Lambe MSc<sup>1</sup>, Peymané Adab MD<sup>1</sup>, Rachel Jordan PhD<sup>1\*</sup>, Alice Sitch MSc<sup>1</sup>, Alexandra Enocson PhD<sup>1</sup>, Kate Jolly PhD<sup>1</sup>, Jen Marsh PhD<sup>1</sup>, Richard D Riley PhD<sup>2</sup>, Martin R Miller MD<sup>1</sup>, Brendan G Cooper PhD<sup>3</sup>, Alice M Turner PhD<sup>4</sup>, Jon Ayres MD<sup>1</sup>, Robert Stockley DSc<sup>4</sup>, Sheila Greenfield PhD<sup>1</sup>, Stanley Siebert PhD<sup>5</sup>, Amanda Daley PhD<sup>1</sup>, KK Cheng FMedSci<sup>1</sup>, David Fitzmaurice PhD<sup>1</sup>, Susan Jowett PhD<sup>1\*</sup>

<sup>1</sup> Institute of Applied Health Research, University of Birmingham, Birmingham, UK

<sup>2</sup> Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK

<sup>3</sup> Respiratory Medicine, University Hospitals Birmingham, Birmingham, UK

<sup>4</sup> Queen Elizabeth Hospital Research Laboratories, Mindelsohn Way, Birmingham, UK

<sup>5</sup> Business School, University of Birmingham, Birmingham, UK

## **Corresponding authors and contact details \***

Dr Rachel Jordan PhD

Reader, University of Birmingham, Birmingham, B15 2TT

Email: [R.E.Jordan@bham.ac.uk](mailto:R.E.Jordan@bham.ac.uk)

Tel: +44 (0)121 414 6775

Dr Sue Jowett PhD

Reader in Health Economics, University of Birmingham, B15 2TT

Email: [s.jowett@bham.ac.uk](mailto:s.jowett@bham.ac.uk)

Tel: +44 (0)121 414 7898

## **Key words**

COPD; Markov model; case-finding; early diagnosis, cost-effectiveness

## Abstract

**Introduction:** “One-off” systematic case finding for COPD using a respiratory screening questionnaire is more effective and cost-effective than routine care at identifying new cases. However, it is not known whether early diagnosis and treatment is beneficial in the longer term. We estimated the long-term cost-effectiveness of a regular case-finding programme in primary care.

**Methods:** A Markov decision-analytic model was developed to compare the cost-effectiveness of a 3-yearly systematic case finding programme targeted to ever smokers aged  $\geq 50$  years with the current routine diagnostic process in UK primary care. Patient-level data on case-finding pathways was obtained from a large RCT. Information on the natural history of COPD and treatment effects was obtained from a linked COPD cohort, UK primary care database and published literature. The discounted lifetime cost per quality-adjusted life year (QALY) gained was calculated from a health service perspective.

**Results:** The incremental cost-effectiveness ratio of systematic case finding versus current care was £16,596 per additional QALY gained, with a 78% probability of cost-effectiveness at a £20,000 per QALY willingness-to-pay threshold. The base case result was robust to multiple one-way sensitivity analyses. The main drivers were response rate to the initial screening questionnaire and attendance rate for the confirmatory spirometry test.

**Discussion:** Regular systematic case-finding for COPD using a screening questionnaire in primary care is likely to be cost-effective in the long-term despite uncertainties in treatment effectiveness. Further knowledge of the natural history of case-found patients and the effectiveness of their management will improve confidence to implement such an approach.

## Key messages

### What is the key question?

What is the long-term cost-effectiveness of undertaking a regular programme of case-finding and early detection of COPD?

### What is the bottom line?

Health economic decision modelling found that systematic case-finding among ever-smokers aged 50 and over on a 3-yearly basis is highly likely to be cost-effective compared with routine practice.

### Why read on?

Currently, case-finding programmes for COPD are not being implemented internationally due to the lack of evidence on the long-term benefits and cost-effectiveness of early diagnosis, and this paper

presents the first analysis of the long-term cost-effectiveness of systematic case-finding for undiagnosed COPD

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most common long-term conditions with significant public health impact, costing over £1.5 billion per annum to the UK NHS<sup>1</sup>, largely due to emergency hospital admissions among patients experiencing exacerbations and costs of maintenance medication<sup>2</sup>. Despite considerable health service use<sup>3</sup> it is thought that perhaps half of all subjects with this disease still remain undiagnosed<sup>4</sup>. Smoking cessation interventions, pharmacotherapy and non-pharmacological approaches such as pulmonary rehabilitation and self-management can reduce morbidity, particularly the frequency of exacerbations, and prolong the life of diagnosed COPD patients<sup>5-9</sup>. Observed benefits might be even greater if undiagnosed patients were found earlier and appropriate treatment commenced, although evidence to support this is currently limited<sup>10</sup>.

A number of small uncontrolled studies of different approaches to identify patients with undiagnosed COPD from primary care and other settings have been undertaken<sup>11</sup>, but there are few appropriately designed trials to address this issue. We recently conducted the largest cluster randomised controlled trial (TargetCOPD)<sup>12</sup> to evaluate two alternative systematic approaches to identify undiagnosed symptomatic patients compared with routine practice (no systematic case-finding). The systematic strategies consisted of opportunistic case-finding, where a respiratory screening questionnaire was administered when eligible patients attended their primary care practice for consultation, and an active approach, where patients were additionally invited by mail to complete the same questionnaire. In both cases, symptomatic patients were then invited for diagnostic spirometry. Over the one-year trial period, active case-finding was the most effective and cost-effective approach to identify new cases (OR=7.5 [95%CI=4.80-11.55]; £333 per additional case detected) compared with routine practice.

Although short-term clinical and cost-effectiveness of a single “one-off” programme of case-finding was demonstrated, this does not necessarily translate into future long-term benefits for a regular programme. Furthermore, the results of the economic analysis (cost per case detected) are not easily comparable with results from other health programmes<sup>13</sup>. In the absence of long-term trial data, model-based economic evaluations are needed<sup>14</sup>. We report the results of a model-based economic evaluation of the long-term costs and benefits of a regular programme of systematic active case-finding over routine practice, using data from the TargetCOPD trial<sup>12</sup>, the linked Birmingham COPD cohort<sup>15</sup>, a large primary care database and the published literature. The model outcome is expressed in cost per quality-adjusted life year (QALY) gained, a measure where a cost-effectiveness decision threshold rule exists in the UK<sup>16</sup>.

## Methods

### Study design and intervention

A Markov decision model was built with TreeAgePro 2015 (TreeAge Software, Williamstown, MA, USA) to estimate the long-term cost-effectiveness of systematic active case-finding for COPD among ever-smokers without a prior diagnosis of COPD in primary care versus routine practice. A cost-utility analysis was undertaken, to calculate the cost per QALY gained from a health service perspective (the UK NHS).

The model was based on the methods in our published case-finding trial, using data from the most effective strategy identified in the trial (“active” case finding) compared with routine care<sup>12 17</sup>. The population in the trial comprised ever smokers aged 40-79 years without a prior diagnosis of COPD. However, for this long-term model, we chose a starting cohort of those aged 50 years, as few patients were identified below this age in the trial<sup>12</sup>.

For the active case-finding approach, eligible patients were identified through electronic health records using a standardised search and their records “flagged”. Flagged patients were offered a respiratory symptom screening questionnaire at any routine practice visit, and were also sent the questionnaire by mail with a reply-paid envelope with up to two reminders. Patients who reported relevant chronic respiratory symptoms on the questionnaire were invited for a confirmatory spirometry test to diagnose COPD according to UK criteria<sup>18</sup>. Routine practice was defined according to UK and international guidance<sup>19</sup>, which recommends spirometric confirmation of COPD among those over the age of 35 years who have a risk factor (generally smoking) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter ‘bronchitis’ or wheeze<sup>18</sup>. Case-finding was a one-off activity in the TargetCOPD trial, but in this study we have assumed that the intervention would be repeated every three years.

### **Model structure**

Patients without a prior COPD diagnosis in each strategy moved between 14 mutually-exclusive health states over their lifetime (Figure 1). The health states were grouped into three broad disease categories: disease-free, undiagnosed disease, diagnosed disease, dead. Patients with no airflow obstruction, either with or without respiratory symptoms, were classified as “disease free”. Those with relevant respiratory symptoms and airflow obstruction were classified as either remaining undiagnosed or becoming diagnosed. A diagnosis required either a new health record of a COPD diagnosis through routine care or receiving a diagnosis through the case-finding programme<sup>18 20</sup>. COPD health states were defined according to the traditional GOLD severity classification with stages 1-4 based on airflow obstruction<sup>21</sup> in line with previous Markov models on the management of COPD<sup>22</sup>. However, the GOLD stage 4 health state was not made available for undiagnosed patients as virtually no patients were newly identified as severe as GOLD stage 4 in previous case-finding studies<sup>11 12</sup>. The model had a time cycle of three months; short enough to capture important COPD-related events such as exacerbations<sup>23</sup>. The time horizon was 50 years assuming a maximum age of 100 years.

The base case starting cohort of patients was distributed across five of the thirteen health states, in line with the patient distribution observed in the TargetCOPD trial for the 50 year old age-group, where 52.7% were male (Table 1)<sup>12</sup>. 43.0% had no respiratory symptoms, 48.2% had symptoms but no airflow obstruction, and the remaining 8.8% were new COPD cases that were undiagnosed prior to participating in the trial. Among these newly-diagnosed patients, 69.0%, 27.4% and 3.6% had COPD GOLD stage 1, 2 and 3 respectively.

| <b>Table 1: General model parameters related to case-finding processes</b>   |              |                            |                             |
|--|--------------|----------------------------|-----------------------------|
| <b>Parameter</b>   | <b>Value</b> | <b><math>\alpha</math></b> | <b><math>\beta</math></b>   |
| <b>Starting cohort characteristics (percentage)<sup>12</sup> <math>\alpha</math></b>   |              |                            |                             |
| Male   | 52.7         | 5999                       | 5394                        |
| Asymptomatic without COPD  | 43.0         | 364                        | 482                         |
| Symptomatic without COPD   | 48.2         | 364                        | 482                         |
| Undiagnosed COPD   | 8.8          | 74                         | 772                         |
| Proportion in GOLD stage 1   | 69.0         | 58                         | 26                          |
| Proportion in GOLD stage 2   | 27.4         | 23                         | 61                          |
| Proportion in GOLD stage 3   | 3.6          | 3                          | 81                          |
| <b>Natural history of development of COPD (percentage per year)</b>  |              |                            |                             |
| Development of symptoms <sup>24 25</sup> #   | 2.0          | 135                        | 6775                        |
| Incidence of COPD <sup>26</sup> § $\alpha$   | 0.6          | 55                         | 9945                        |
| Proportion of incident cases in GOLD stage 1 <sup>27</sup> ‡   | 72.2         | 44                         | 17                          |
| Proportion of incident cases in GOLD stage 2 <sup>27</sup> ‡   | 27.8         | 17                         | 44                          |
| <b>Routine practice (percentage)<sup>12</sup></b>  |              |                            |                             |
| Probability of being diagnosed with COPD   | 0.8          | 337                        | 41692                       |
| Treatment after COPD diagnosis   | 29.3         | 3972                       | 9585                        |
| <b>Systematic case-finding activities (percentage)<sup>12</sup></b>  |              |                            |                             |
| Received questionnaire   | 99.9         | 12175                      | 1                           |
| Responded to questionnaire   | 35.5         | 846                        | 1572                        |
| Reported symptom on questionnaire among responders   | 56.4         | 482                        | 364                         |
| Spirometry conducted in those reporting symptoms   | 66.1         | 559                        | 287                         |
| Diagnosed with COPD in those attending spirometry  | 39.8         | 87                         | 2331                        |
| <b>Utility</b>   |              |                            |                             |
| Asymptomatic without COPD <sup>15</sup>  | 0.8394       | 1522                       | 291                         |
| Symptomatic without COPD <sup>15</sup>   | 0.7549       | 8817                       | 2862                        |
| <b>Costs (£)<sup>12</sup></b>  |              |                            |                             |
|  | <b>Value</b> | <b><math>\alpha</math></b> | <b><math>\lambda</math></b> |
| Postal questionnaire   | 4.01         | 99                         | 39                          |
| Booking and conducting spirometry test   | 55.27        | 24                         | 0.5                         |
| ‡ Cohort study of Danish general population at year 0, 5 and 15 (Copenhagen City Heart Study). Of symptomatic normal at baseline that later developed COPD 15 years later, 72% and 28% had GOLD stage 1 and 2 respectively. This was assumed to be a fixed distribution                          |              |                            |                             |
| # Based on clinical opinion, it was considered that incident cases account for 10% of prevalent cases (20%) of respiratory symptoms in the UK population, which was validated using values from Eagan (2002).  |              |                            |                             |
| § A longitudinal observational primary care database (Dutch Integrated Primary Care Information [IPCI]) follow-up study. The incidence rate was reported in 1000 person-years, which was then converted to one-year probability.   |              |                            |                             |
| $\alpha$ Age dependent parameters. Values presented are for 50-year-olds   |              |                            |                             |
| <b>Beta distribution:</b> The symbols $\alpha$ and $\beta$ are parameters that define a beta distribution, which is a continuous probability distribution bounded at the extremes by 0 and 1. The number of successes is $\alpha$ while failure is $\beta$ .                                     |              |                            |                             |
| <b>Gamma distribution:</b> The symbols $\alpha$ and $\lambda$ are parameters that define a gamma distribution, which is a continuous discrete distribution bounded at the extremes by 0 and $\infty$ . The mean of the distribution is $\alpha(1/\lambda)$ and variance is $\alpha(1/\lambda)^2$ |              |                            |                             |

Transitions at every 3-month cycle were based on several assumptions to approximate the natural history and current management of COPD. Only patients who had developed symptoms could progress to any of the categories of undiagnosed COPD. Once a patient developed COPD, the model allowed movement to the immediate next worse GOLD stage. Direct deterioration beyond the next stage within a three-month period was not allowed because COPD was assumed to progress slowly (e.g. movements from GOLD 1 directly to 3 and from GOLD 2 to 4 were not allowed). Transition from an undiagnosed to a diagnosed health state was permitted, but not the reverse. Not all diagnosed patients received treatment (Figure 2). Improvements were only permitted in treated patients. Undiagnosed GOLD stage health states were assumed to have the same baseline transitions to worse undiagnosed GOLD stages as diagnosed health states. Finally, there was a risk of exacerbation and death in a 3-month time cycle within any health state. The case-finding processes were modelled as events within each health state (Figure 1). Systematic case-finding only occurred every three years, although a new diagnosis of COPD could arise through routine care in either strategy in every cycle.

### **Data values used in the model**

Most of the data related to the process of case finding and diagnosis of COPD were derived from the active arm of the TargetCOPD trial<sup>12</sup> and the associated Birmingham COPD cohort study<sup>15</sup> (Table 1 Table 2). Transition probabilities between GOLD stages were obtained from The Health Improvement Network (THIN) database, which holds longitudinal primary care information on over 11 million UK patients, including about 2 million with diagnosed COPD<sup>28</sup> (See Supplementary material for detailed estimation methods).

**Table 2: Model parameters related to disease progression and outcomes (per annum)**

|  | GOLD 1  | GOLD 2  | GOLD 3  | GOLD 4  | Dead     |
|--|---------|---------|---------|---------|----------|
| <b>Transitions (probability)<sup>28 ‡</sup></b>        |         |         |         |         |          |
| GOLD 1   | 0.9047  | 0.0876  | 0.0000  | 0.0000  | 0.0077   |
| GOLD 2   | 0.0510  | 0.9001  | 0.0362  | 0.0000  | 0.0128   |
| GOLD 3   | 0.0000  | 0.1044  | 0.8368  | 0.0324  | 0.0265   |
| GOLD 4   | 0.0000  | 0.0000  | 0.0936  | 0.8187  | 0.0877   |
| <b>Transition for symptomatic patients<sup>‡</sup></b> |         |         |         |         |          |
| Symptoms, no COPD <sup>26 27</sup>                     | 0.0040  | 0.0015  | 0.0000  | 0.0000  | 0.0026** |
| <b>Exacerbation (probability)</b>                      |         |         |         |         |          |
| Severe exacerbation <sup>15*</sup>                     | 0.0270  | 0.0760  | 0.2720  | 0.3480  | -        |
| Mortality after severe exacerbation <sup>29</sup>      | 0.0703  | 0.0703  | 0.0703  | 0.0703  | -        |
| <b>Treatment effect (Odds ratio)</b>                   |         |         |         |         |          |
| All-cause mortality <sup>30</sup>                      | 0.9800  | 0.9800  | 0.9800  | 0.9800  | -        |
| Severe exacerbation <sup>30</sup>                      | 0.8500  | 0.8500  | 0.8500  | 0.8500  | -        |
| Progression to the next GOLD stage <sup>‡</sup>        | 0.8500  | 0.8500  | 0.8500  | 0.8500  | -        |
| <b>Costs (£) <sup>†</sup></b>                          |         |         |         |         |          |
| Scheduled GP and hospital visits <sup>19</sup>         | 164.56  | 267.06  | 394.01  | 541.06  | -        |
| Inhaled medication <sup>29</sup>                       | 485.16  | 567.84  | 735.96  | 824.52  | -        |
| Inpatient stay due to exacerbation <sup>29</sup>       | 2263.00 | 2263.00 | 2263.00 | 2263.00 | -        |
| <b>Health outcomes</b>                                 |         |         |         |         |          |
| Utility <sup>15*</sup>                                 | 0.7197  | 0.7013  | 0.6798  | 0.5855  | -        |
| Disutility from severe exacerbation <sup>15*</sup>     | -0.2398 | -0.2337 | -0.2265 | -0.1951 | -        |
| Utility gained from treatment <sup>31</sup>            | 0.0367  | 0.0367  | 0.0367  | 0.0367  | -        |

<sup>†</sup> Cost method was adapted and unit costs were updated to 2015 price year.

<sup>‡</sup> Age depended parameters. Values presented are for 50-year-olds

\* Birmingham COPD cohort: Unpublished data from the Birmingham Lung Improvement StudieS – an ongoing series of studies aimed at evaluating better strategies for identifying and managing COPD in primary care. Disutility data shows utility loss over one year: 50% utility loss in the first month and 25% utility loss for the second and third month per cycle. The impact of exacerbations on quality of life is greater in patients with less severe disease who also tend to be younger<sup>32</sup>.

\*\* Value represents mortality risk in the general population

<sup>‡</sup> Expert panel comprised consultant pulmonologists, epidemiologists and senior health economist. The panel was presented with results of prior scoping reviews on the effect of treatment on exacerbation, mortality and lung function, but there was no review transition between GOLD stages. Given that the odds ratio in reviews were around 0.85, the panel agreed then that the odds of treatment slowing disease progression to the next worse GOLD stage should be 0.85 for the base case.

For pragmatic reasons, only severe exacerbations (i.e. those requiring in-patient stay<sup>33</sup>) were considered in this evaluation as these episodes alone account for over 84% of all COPD related healthcare costs<sup>34</sup>. The annual rate of severe exacerbations by undiagnosed and diagnosed GOLD stage was obtained from unpublished baseline data from the Birmingham cohort<sup>15</sup>. The rates were converted to quarterly transition probabilities and beta distributions were fitted about the point estimates.

Age and sex specific all-cause mortality rates were obtained from the life tables for England and Wales<sup>35</sup> and applied to patients without COPD (Table S1). Rates were adjusted to avoid double counting COPD-related mortality. Age specific all-cause mortality rates for diagnosed COPD patients were derived from



the annual transition matrix generated from the THIN database (Table S7). COPD-adjusted all-cause mortality for the “disease free” cohort was derived from the UK life tables (Table S1).

Prescription patterns in UK primary care show 29.6% of COPD patients receive a LABA-based inhaled medication (excluding LAMA), 9.5% receive a LAMA-based combination (excluding LABA), and 25.0% receive combinations that include LABA+LAMA<sup>36</sup>. Treatment effects from published systematic reviews suggest reductions in risk of exacerbations of up to 27% (OR=0.73) for some dual inhaler combinations with further reductions for triple drug combinations<sup>9</sup>. It was not practical to model treatment effects for each COPD inhaler combination on each type of outcome, therefore, a conservative simplifying assumption was made, using the point estimates from a meta-analysis of the effect of a single LAMA versus placebo on mortality (OR=0.98) and severe exacerbation (OR=0.85)<sup>30</sup>. The published evidence was largely based on patients with a forced expiratory volume in 1 second (FEV<sub>1</sub>)<60%, but the effect was assumed to be similar across all GOLD stages, although emerging evidence shows that patients with FEV<sub>1</sub>>60% may have even greater capacity to benefit from early treatment<sup>37</sup>.

Only 29.3% of newly diagnosed patients were modelled to commence treatment annually<sup>36</sup>. This annual rate was derived from a study that showed 82.7% of COPD patients in the UK were on treatment 5 years post diagnosis. This is likely to be a conservative estimate as reports from other countries suggest treatment initiation rates to be higher<sup>38</sup>.

Utility values for undiagnosed and diagnosed GOLD stages 1 to 4 health states were derived from unpublished baseline data from the Birmingham cohort<sup>15</sup>, containing patients representative of a UK primary care COPD population in a stable condition and also symptomatic individuals without COPD. For individuals without symptoms; utility values were derived from a published age-adjusted algorithm, developed from utility values from the general population<sup>39</sup>, as there was no utility value for ever-smokers in the general population in the literature. The model assumed that utility loss following severe exacerbation persisted for three months, in line with a previously published model<sup>29</sup>. Disutility was modelled to be higher in the first month (50%) compared to the second (25%) and third (25%) month, after which quality of life was assumed to return to pre-exacerbation levels. This loss was applied to mean utility scores across all the four COPD severity levels<sup>40 41</sup>.

**Resource use and costs:** The cost of systematic case-finding was estimated from the active arm of the TargetCOPD trial<sup>12</sup> (Table 1, Table 2, Table S3, Table S4, Table S5). Estimation of healthcare costs for the diagnosed and treated GOLD stages (Table 2) followed existing costing frameworks<sup>29 41</sup>. Cost of COPD-related inhaled pharmacotherapy was calculated using data from diagnosed patients in the Birmingham cohort. No cost was attached to routine care or comorbidities since these were assumed to be the same for both arms.

Unit costs were primarily from the Personal Social Services Research Unit (PSSRU)<sup>42</sup>, NHS reference costs and the British National Formulary<sup>43</sup>. Costs were inflated to 2015 prices using the Hospital and Community Health Services (HCHS) inflation index<sup>42</sup> where necessary.

### Assessment of cost-effectiveness

An incremental cost-effectiveness ratio (ICER) was calculated as a ratio of the mean difference in cost and the mean difference in QALY gained between systematic case-finding and routine practice and presented as cost per QALY gained. Discounting was applied to costs and outcomes at a rate of 3.5% in line with NICE guidance<sup>16</sup>. Where available, data were entered into the model as distributions in order to fully incorporate the uncertainty around parameter values, so that a probabilistic sensitivity analysis could be undertaken. A gamma distribution was fitted for all cost parameters. A lognormal distribution, which accommodates the ratio nature of risk measures, was constructed for odds ratios. Beta distributions were fitted for all transition probabilities and utility estimates. The probabilistic sensitivity analysis was run with 10,000 simulations, and cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) were produced. The CEAC is the standard method for quantifying the likelihood that an intervention is more cost-effective compared to an alternative.

### Additional one-way sensitivity analyses

A series of one-way sensitivity analyses was conducted to assess how key parameters such as starting age of cohort, screening interval and time horizon affected the results. The impact of other important parameters such as questionnaire response rate, spirometry attendance rate, treatment initiation rates and the effectiveness of treatment with regards to exacerbations, mortality and quality of life gain were also explored.

## Results

The base-case results for 50-year old ever smokers (Table 3) showed that compared to routine practice, a three-yearly systematic active case-finding strategy was more expensive but more effective, with a greater number of QALYs gained over a lifetime time horizon. The difference in cost was £466, with 0.0281 QALYs gained, producing an ICER of £16,596 per QALY gained.

**Table 3 Base-case result Cost-Utility Analysis**

| Case-finding strategy   | Mean values |         | Mean difference |        | ICER      |
|-------------------------|-------------|---------|-----------------|--------|-----------|
|                         | Cost (£)    | QALYs   | Cost (£)        | QALY   | (£/QALY)  |
| Routine care            | 1,007.64    | 14.1767 |                 |        |           |
| Systematic case-finding | 1,473.51    | 14.2048 | 465.87          | 0.0281 | 16,596.28 |

Results from the probabilistic sensitivity analysis (Figure 3) showed all 10,000 resampled points were clustered in the North-East quadrant, representing instances where systematic case-finding was more expensive and more effective than routine practice. 78.4% of these points were below the

£20,000/QALY willingness-to-pay threshold (WTP)<sup>16</sup>, which represents the probability of systematic case-finding being cost-effective at that threshold. The CEAC shows the probability of cost-effectiveness at different WTP thresholds (Figure S1)

### **Sensitivity analysis**

Varying the age for starting screening altered both the intervention costs and the QALYs gained (Table 4). The most cost-effective age to begin screening in UK ever-smokers was estimated to be 60 years. Although the intervention costs were higher, the QALY gains from management of symptoms were also greater. Compared to younger age groups, a higher proportion of 60-year-olds had developed COPD during the first case-finding cycle, and therefore did not incur the costs associated with case-finding in subsequent cycles. The 60-year-olds were also young enough to maximally benefit from treatment of their symptoms relative to older cohorts.

Annual case-finding yielded the most benefit but was the most expensive strategy, whilst a screening interval of ten years had the lowest ICER thereby making the preferred screening interval from a cost-effectiveness perspective. The sensitivity analysis results also showed that the minimum required screening questionnaire response rate was 12% for systematic case-finding to remain cost-effective at the £20,000 per QALY threshold. Similarly, systematic case-finding was only preferred to routine practice if more than 26% of those who were invited for spirometric confirmation attended the session.

| Table 4: Sensitivity analysis results   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
|   | Cost difference | QALY difference | ICER (£/QALY)    |
| <b>Cohort Age</b>   |                 |                 |                  |
| 40 years  | 356.32          | 0.0184          | 19,373.50        |
| <b>50 years</b>   | <b>465.87</b>   | <b>0.0281</b>   | <b>16,596.28</b> |
| 60 years  | 520.27          | 0.0333          | 15,645.62        |
| 70 years  | 448.61          | 0.0265          | 16,915.53        |
| <b>Screening Interval</b>   |                 |                 |                  |
| 1 year  | 910.08          | 0.0465          | 19,586.35        |
| <b>3 years</b>  | <b>465.87</b>   | <b>0.0281</b>   | <b>16,596.28</b> |
| 5 years   | 334.09          | 0.0210          | 15,922.52        |
| 10 years  | 217.00          | 0.0143          | 15,219.88        |
| <b>Time horizon</b>   |                 |                 |                  |
| 20 years  | 316.94          | 0.0147          | 21,522.47        |
| 30 years  | 411.87          | 0.0226          | 18,206.16        |
| 40 years  | 458.44          | 0.0272          | 16,883.96        |
| <b>50 years</b>   | <b>465.87</b>   | <b>0.0281</b>   | <b>16,596.28</b> |
| <b>Spirometry attendance rate</b>   |                 |                 |                  |
| 10.5% (Threshold 2)   | 159.21          | 0.0054          | 29,556.13        |
| 26.3 % (Threshold 1)  | 260.33          | 0.0130          | 20,097.49        |
| <b>66.1% (Base case)</b>  | <b>465.87</b>   | <b>0.0281</b>   | <b>16,596.28</b> |
| <b>Questionnaire response rate</b>  |                 |                 |                  |
| 4.0% (Threshold 2)  | 122.88          | 0.0040          | 30,364.90        |
| 11.6% (Threshold 1)   | 219.19          | 0.0109          | 20,056.90        |
| <b>35.0% (Base case)</b>  | <b>465.98</b>   | <b>0.0281</b>   | <b>16,595.80</b> |
| <b>Utility gain from treatment</b>  |                 |                 |                  |
| 0.0000  | 465.87          | 0.0115          | 40,456.80        |
| 0.0092 (Threshold 2)  | 465.87          | 0.0155          | 30,011.41        |
| 0.0269 (Threshold 1)  | 465.87          | 0.0233          | 19,999.67        |
| <b>0.0367 (Base case)</b>   | <b>465.87</b>   | <b>0.0281</b>   | <b>16,596.28</b> |
| Threshold 1= Willingness-to-pay threshold at £20,000 per QALY   |                 |                 |                  |
| Threshold 2= Willingness-to-pay threshold at £30,000 per QALY   |                 |                 |                  |
| Questionnaire response rate after the initial invite in the TargetCOPD trial = 15% (2312/15387) <sup>Error! Reference source not found.</sup> |                 |                 |                  |
| Questionnaire response rate after the first reminder in the TargetCOPD trial = 25% (3936/15387) <sup>Error! Reference source not found.</sup> |                 |                 |                  |
| Base case values are in bold fonts  |                 |                 |                  |

The model was also sensitive to the effectiveness of treatment on disease outcomes. The opportunity cost of systematic case-finding steadily increased as the effect of treatment worsened (Figure 4). Firstly, each variable was considered separately. When no impact on mortality was assumed, case-finding was still cost-effective at £17,663/QALY. No impact on exacerbations gave an ICER of £18,258/QALY. However, if no impact on progression (to worse GOLD stage) was assumed, the ICER rose to £22,943/QALY, and the threshold odds ratio for cost-effectiveness at £20,000/QALY was 0.94. When the odds ratios for the effectiveness of treatment on all outcomes were simultaneously adjusted to 1,

systematic case finding was not preferred over routine practice (Figure S2), with an ICER of £28,811/QALY.

The model was also sensitive to the magnitude of the additional impact on quality of life which was independent of the impact on quality of life and survival from progression, mortality and exacerbation (Table 4). If the utility gain reduced to less than 0.0269, then systematic case finding was no longer cost-effective at £20,000/QALY. Assuming treatment had no additional impact on quality of life resulted in an ICER of £40,457/QALY. Another important determinant of cost-effectiveness was the treatment initiation rate. A systematic case-finding programme was cost-effective as long as treatment was initiated in at least 8% of previously untreated patients yearly (Figure 4).

## Discussion

There are as yet no published primary studies which provide data on the long-term cost-effectiveness of a systematic programme of case finding for undiagnosed COPD. In their absence, this novel economic model aims to address this unanswered question using data from the best published and unpublished sources available. We have shown that the systematic screening of ever-smokers aged 50 years and over, every 3 years is potentially a cost-effective strategy according to UK cost-effectiveness thresholds. The results were supported by the majority of the sensitivity analyses except in the most extreme scenarios. For case-finding to be cost-effective, a sufficient proportion of patients must respond to the initial screening questionnaire (12%) and attend the confirmatory spirometry test (26%). In our published trial, 15% responded after the initial invite without a reminder<sup>12</sup> and more than 63% of those invited attended the spirometry test. Crucially, one in twelve (8%) of previously untreated patients must also be started on treatment yearly for systematic case-finding to remain cost-effective. Unpublished data from long term follow up for the Target COPD trial suggests that twelve months after diagnosis, 21% of case-found patients in the active case-finding arm were on the practice COPD QOF register, suggesting they were likely to be receiving some treatment. Mean lifetime costs for both systematic case finding and routine care are relatively low (less than £1,500), however this can be explained by the low incidence of COPD and a relatively low proportion of undiagnosed COPD in the starting cohort. Therefore only a relatively small proportion of patients in the model will develop COPD over time and incur costs. Furthermore, in the case finding strategy, as approximately only a third of patients respond to the questionnaire, only a small proportion will actually go onto receive spirometry and incur these additional costs.

We sought to explain why systematic case-finding was cost-effective despite the use of conservative assumptions, especially for treatment effectiveness. First, as our systematic case finding approach was relatively inexpensive, only a small proportion of newly diagnosed patients needed to benefit from

treatment for the intervention to be cost-effective. Second, once treatment commenced, the risk of exacerbation and mortality were simultaneously reduced. Fewer exacerbations result in lower loss in QALYs as well as cost savings from fewer admissions to hospital. Reduced risk of mortality among treated patients results in greater accumulation of QALYs compared to their untreated counterparts. Overall, mortality did not have a significant impact on the ICER because treated patients who survived longer also consumed more healthcare resources. There are also further benefits from the effect of treatment on disease progression, and we also assumed a small utility benefit of being on treatment independent of disease progression and exacerbations. If this additional benefit was removed, then case-finding was no longer cost-effective.

Ten yearly systematic active case-finding was the most cost-effective screening interval, although policymakers need to balance this against a greater proportion of the cohort remaining undiagnosed for longer and the value patients and practitioners place on early diagnosis<sup>44</sup>.

To the best of our knowledge this is the first model to evaluate the long-term cost-effectiveness of a COPD case-finding strategy. The reliability of the main data sources that informed the model was a notable strength. Patient-level data from the TargetCOPD trial, the Birmingham COPD cohort, and THIN dataset provided up-to-date information on both diagnosed and undiagnosed COPD patients in primary care in the UK.

Another strength was the use of conservative estimates of the treatment effect to prevent overestimation of the benefits of systematic case-finding. The natural history of COPD in untreated patients remains largely unknown. Here, we assumed that untreated and treated patients had the same natural history. In reality, undiagnosed patients may have a slightly poorer quality of life from sub-optimal management and the disease progression rate might be faster<sup>3 36</sup>.

This study, however does have several limitations. The first limitation is the uncertainty around the effect of treatment on progression from one GOLD stage to the next<sup>45 46</sup>. This estimate was not available in the literature. Although some previous studies have shown that treatment slows lung function decline (for example changes in FEV<sub>1</sub>)<sup>47 48</sup>, there is currently no clear method for transforming changes in FEV<sub>1</sub> decline into risk ratios that could be used in this model. Nonetheless, the reduced lung function decline in treated patients is an indication that treatment may reduce risk of progressing to a worse GOLD stage. However, in order to explore the uncertainty regarding the impact of treatment, extensive sensitive analyses were undertaken.

Additionally, the treatment effect as used in this model only captured the benefits associated with inhaled medications. Other interventions such as smoking cessation which has been shown to be effective in reducing COPD progression<sup>49</sup>, pulmonary rehabilitation<sup>8</sup> and self-management<sup>41</sup> which

improve HRQoL and reduce exacerbations, were not considered. Inclusion of other interventions would have made systematic case-finding more cost-effective but few patients receive these interventions, thereby making their wider benefit uncertain.

Another possible weakness is the use of the traditional GOLD staging criteria<sup>50</sup> as airflow obstruction relates only weakly to quality of life. For instance, some patients with GOLD stage 2 may experience worse symptoms and impact than those with GOLD stage 3. Other symptom-based classification systems that are better predictors of prognosis now exist<sup>51</sup>. However there is no consensus regarding the most appropriate staging criteria and the GOLD staging used here was the one used in previous literature which has informed inputs for assumptions used in the model.

We have also assumed that transitions between GOLD stages, exacerbation rates and utility values for undiagnosed states are the same as diagnosed (and untreated) GOLD stage health states. However, this assumption is supported by findings from cohort studies (e.g. the Can COLD study) that show that those with undiagnosed COPD have similar rates of health service use related to respiratory disease as those who have diagnosed COPD<sup>3</sup>.

Despite this, a further weakness lies in the assumption made regarding costs of undiagnosed disease. Only COPD-related costs are taken into account rather than all-cause costs. This may underestimate costs in the undiagnosed states, where there may be greater health care utilisation (e.g. primary care visits) due to COPD but the costs are not yet related to the condition. We also assume that untreated patients do not incur any healthcare cost until an admission for severe exacerbation occurs, whereas it is likely that some would have received prescriptions for their symptoms. However, it would be difficult to estimate these additional health care costs, and the conservative approach we have taken means that it is likely that case-finding would be more cost-effective with their inclusion.

A significant barrier to the implementation of case-finding programmes around the world has been the lack of evidence on whether the long term benefit of early diagnosis and treatment outweighs the associated cost. Our economic model suggests that systematic case finding leading to earlier diagnosis and treatment would provide benefits and value for money, despite uncertainty about treatment effectiveness in case-found patients and those with mild disease. The treatments would have to be almost completely ineffective on all important disease outcomes for regular case-finding to be a worse option than current practice. However, we recognise that this is not a primary study, and it would be strengthened by better knowledge about the natural history of the disease and treatment effectiveness. Ultimately, data from a case-finding trial with longer-term health outcomes would provide more robust evidence. We have also provided information on potential starting age and screening intervals. The exact configuration of such case-finding activity may however depend on local factors such as competing pressures on national budgets. A further need is to explore more fully patient views on earlier

diagnosis and the overall financial impact on primary healthcare organisations of a much larger population of COPD patients to manage. Should a new programme of case-finding be implemented, a clear pathway of care would need to be provided in order to ensure newly diagnosed patients are optimally treated, as current data suggest that this is seldom the case<sup>37</sup>.

## Conclusion

We conclude that a three-yearly systematic approach to case-finding is likely to be cost-effective in the long term given the current management of COPD patients in primary care setting. The true importance of early diagnosis and treatment of COPD will be better understood as more evidence emerges on the effect of treatment on COPD and the longer-term results of case-finding trials are available. Longer-term follow-up of newly diagnosed patients may also further clarify the natural history of COPD.

## Figure legends

**Figure 1: Transitions between model health states**

**Figure 2: Example of pathway for an undiagnosed patient with GOLD stage 3 during a 3-month systematic case-finding cycle**

**Figure 3 Cost-effectiveness plane for the comparison of systematic case-finding with routine care, based on 10,000 cost-effect pairs**

**Figure 4: Multiple one-way sensitivity analyses showing the relationship between ICER and (1) the effect of treatment on exacerbation (2) the effect of treatment on Mortality (3) the effect of treatment on disease progression (4) the yearly treatment initiation rate in newly diagnosed patients. Treatment effectiveness estimates are expressed as odds ratios.**



## NOTES

### Acknowledgements

This paper summarises independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research (grant reference number RP-PG-0109-10061). The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health. The original TargetCOPD trial was part of the Birmingham Lung Improvement Studies (BLISS) and we thank the GPs, patients and BLISS research team for making the trial possible, and Andy Dickens for providing data from the BLISS cohort study. We thank IMS Health for use of the THIN data.

### Declared interests

KKC reports grants from Pfizer China, outside of the submitted work. RS reports personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Chiesi, personal fees from Takeda, personal fees from Novartis, personal fees from Polyphor, grants from CSL Behring, grants from Talecris, and personal fees from Dyax, outside of the submitted work. AMT reports grants from Linde REAL fund, grants from Alpha 1 Foundation, non-financial support from GSK, non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, and personal fees and non-financial support from AZ, outside of the submitted work. SJ, PA, REJ, KKC, MRM KJ, RDR, DF, SS, AD, BGC, RS, JA and SG report grants from NIHR, during the conduct of the study. Other authors declare no competing interests.

### Contributions of Authors

**Tosin Lambe (TL)** Built the model, conducted the economic analysis and wrote the paper with guidance from SJ, REJ and PA. **(SJ)** designed the health economic analyses for the TargetCOPD trial, supervised the economic modelling, and contributed to writing the paper. **Peymané Adab (PA)** and **Rachel E Jordan (REJ)** identified the need for the TargetCOPD trial, co-led the running of the trial, provided guidance on the input parameters for the model, and contributed to writing the paper. **David Fitzmaurice (DF)** provided a primary care perspective and supported enrolment of practices for the trial. **KK Cheng (KKC)** contributed to refining the TargetCOPD trial design that generated data for parameter inputs. **Alice Sitch (AS)** undertook the statistical analyses with guidance and input from **Richard D Riley (RDR)** and **Jen Marsh (JM)**. **Alexandra Enocson (AE)**, **REJ**, **PA** and **DF** oversaw the TargetCOPD trial. **Alice M Turner (AMT)** provided clinical expertise related to model data inputs. **Kate Jolly (KJ)**, **Martin R Miller (MRM)**, **Brendan G Cooper (BGC)**, **Robert Stockley (RS)** provided expert guidance on the natural history of COPD, spirometry training/quality and model pathways. PA, REJ, DF, JA, KKC, SJ, KJ, RDR, MRM, BGC, RS, SG, SS, AD, JM as the

original co-investigator team had input in the study set up. All authors had input into the analysis and interpretation of the model, and edited the manuscript.

## References

1. McLean S, Hoogendoorn M, Hoogenveen RT, et al. Projecting the COPD population and costs in England and Scotland: 2011 to 2030. *Sci Rep* 2016;6:31893. doi: 10.1038/srep31893 [published Online First: 2016/09/02]
2. Mahon J, Bartlett C, Isojarvi J, et al. Literature review: the economic costs of lung disease and the cost effectiveness of policy and service interventions [Report of literature review]. British Lung Foundation; 2017 [updated October 2017. Available from: <https://www.brit-thoracic.org.uk/document-library/research-and-innovation/documents/literature-review-the-economic-costs-of-lung-disease/> accessed 25 April 2018.
3. Labonte LE, Tan WC, Li PZ, et al. Undiagnosed Chronic Obstructive Pulmonary Disease Contributes to the Burden of Health Care Use. Data from the CanCOLD Study. *Am J Respir Crit Care Med* 2016;194(3):285-98. doi: 10.1164/rccm.201509-1795OC [published Online First: 2016/02/03]
4. Jordan RE, Lam KB, Cheng KK, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. *Thorax* 2010;65(6):492-8. doi: 10.1136/thx.2009.129395 [published Online First: 2010/06/05]
5. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015(2):CD003793. doi: 10.1002/14651858.CD003793.pub3 [published Online First: 2015/02/24]
6. Zwerink M, Brusse-Keizer M, van der Valk PD, et al. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014(3):CD002990. doi: 10.1002/14651858.CD002990.pub3 [published Online First: 2014/03/26]
7. Godtfredsen NS, Vestbo J, Osler M, et al. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. *Thorax* 2002;57(11):967-72. [published Online First: 2002/10/31]
8. Puhan MA, Gimeno-Santos E, Cates CJ, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016;12:CD005305. doi: 10.1002/14651858.CD005305.pub4 [published Online First: 2016/12/09]
9. Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013(11):CD003794. doi: 10.1002/14651858.CD003794.pub4 [published Online First: 2013/11/12]
10. Guirguis-Blake JM, Senger CA, Webber EM, et al. Screening for Chronic Obstructive Pulmonary Disease: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2016;315(13):1378-93.
11. Haroon SM, Jordan RE, O'Beirne-Elliman J, et al. Effectiveness of case finding strategies for COPD in primary care: a systematic review and meta-analysis. *NPJ Prim Care Respir Med* 2015;25:15056.
12. Jordan RE, Adab P, Sitch A, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. *The Lancet Respiratory Medicine* 2016;4(9):720-30.
13. Van Boven J. COPD case finding: effective, but also cost-effective? *Lancet Respir Med* 2016;4(10):49.
14. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: OUP Oxford 2006.

15. Adab P, Fitzmaurice DA, Dickens AP, et al. Cohort Profile: The Birmingham Chronic Obstructive Pulmonary Disease (COPD) Cohort Study. *Int J Epidemiol* 2017;46(1):23. doi: 10.1093/ije/dyv350 [published Online First: 2016/07/06]
16. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal. In: NICE, ed. United Kingdom: NICE, 2013.
17. Jordan RE, Adab P, Jowett S, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. *BMC Pulm Med* 2014;14:157. doi: 10.1186/1471-2466-14-157 [published Online First: 2014/10/05]
18. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline [NG115]: NICE; 2018 [Available from: <https://www.nice.org.uk/guidance/NG115> accessed December 2018.
19. National Institute for Health and Care Excellence (NICE). Chronic Obstructive Pulmonary Disease (COPD) costing report: Implementing NICE guidance [CG101]. London, United Kingdom WC1V 6NA: National Institute for Health and Care Excellence (NICE),, 2011.
20. Agusti A, Celli BR, Chen R, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (2018 Report). GOLD strategy: Global Initiative for Chronic Obstructive Lung Disease, Inc (GOLD), 2018.
21. GOLD. 2015 report: Global Strategy for the Diagnosis, Management, and Diagnosis of Chronic Obstructive Pulmonary Disease (GOLD) 2015 [Available from: [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2015\\_Sept2.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Sept2.pdf). [Archive <https://goldcopd.org/archived-reports/>] accessed 10 October 2015.
22. Hoogendoorn M, Feenstra TL, Asukai Y, et al. Cost-effectiveness models for chronic obstructive pulmonary disease: cross-model comparison of hypothetical treatment scenarios. *Value Health* 2014;17(5):525-36. doi: 10.1016/j.jval.2014.03.1721 [published Online First: 2014/08/17]
23. Hoogendoorn M, Feenstra TL, Hoogenveen RT, et al. Association between lung function and exacerbation frequency in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2010;5:435-44.
24. NatCen Social Research RFaUCMS, Department of Epidemiology and Public Health,. Health Survey for England, 2010. [data collection]. [data collection]. 3rd Edition. UK Data Service. SN: 6986. <http://doi.org/10.5255/UKDA-SN-6986-3>, 2015.
25. Eagan TM, Bakke PS, Eide GE, et al. Incidence of asthma and respiratory symptoms by sex, age and smoking in a community study. *Eur Respir J* 2002;19(4):599-605. [published Online First: 2002/05/10]
26. Afonso AS, Verhamme KM, Sturkenboom MC, et al. COPD in the general population: prevalence, incidence and survival. *Respir Med* 2011;105(12):1872-84. doi: 10.1016/j.rmed.2011.06.012 [published Online First: 2011/08/20]
27. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002;166(3):329-32.
28. James GD, Donaldson GC, Wedzicha JA, et al. Trends in management and outcomes of COPD patients in primary care, 2000-2009: a retrospective cohort study. *NPJ Prim Care Respir Med* 2014;24:14015. doi: 10.1038/npjpcrm.2014.15 [published Online First: 2014/07/06]
29. Dretzke J, Blissett D, Dave C, et al. The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. *Health Technol Assess* 2015;19(81):1-246.
30. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014(7):CD009285. doi: 10.1002/14651858.CD009285.pub3 [published Online First: 2014/07/22]
31. Briggs AH, Lozano-Ortega G, Spencer S, et al. Estimating the cost-effectiveness of fluticasone propionate for treating chronic obstructive pulmonary disease in the presence of missing

- data. *Value Health* 2006;9(4):227-35. doi: 10.1111/j.1524-4733.2006.00106.x [published Online First: 2006/08/15]
32. Menn P, Weber N, Holle R. Health-related quality of life in patients with severe COPD hospitalized for exacerbations - comparing EQ-5D, SF-12 and SGRQ. *Health Qual Life Outcomes* 2010;8:39.
  33. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117(5 Suppl 2):398S-401S.
  34. Starkie HJ, Briggs AH, Chambers MG. Pharmacoeconomics in COPD: lessons for the future. *Int J Chron Obstruct Pulmon Dis* 2008;3(1):71-88.
  35. Office for National Statistics (ONS). Death registrations summary tables - England and Wales: Office for National Statistics (ONS),; 2016 [updated July 18, 2018. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables> accessed November 24 2017.
  36. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis* 2014;9:889-904.
  37. Zhou Y, Zhong NS, Li X, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017;377(10):923-35.
  38. Barrecheguren M, Monteagudo M, Ferrer J, et al. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. *Respiratory Medicine* 2016;111:47-53.
  39. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13(5):509-18.
  40. Rutten-van Molken MP, Oostenbrink JB, Miravittles M, et al. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. *Eur J Health Econ* 2007;8(2):123-35.
  41. Jordan RE, Majothi S, Heneghan NR, et al. Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. *Health Technol Assess* 2015;19(36):1-516. doi: 10.3310/hta19360 [published Online First: 2015/05/20]
  42. Curtis LA, Burns A. Unit Costs of Health and Social Care 2015 Canterbury, UK: Personal Social Services Research Unit, University of Kent; 2015 [accessed October 27 2015].
  43. British National Formulary (BNF). Guidance on actions and uses of drugs prescribed in the UK: BNF; 2016 [Available from: <https://bnf.nice.org.uk/> accessed February 19 2016].
  44. Summers RH, Sharmeen T, Lippiett K, et al. A qualitative study of GP, nurse and practice manager views on using targeted case-finding to identify patients with COPD in primary care. *NPJ Prim Care Respir Med* 2017;27(1):49.
  45. Rennard SI, Vestbo J. Natural histories of chronic obstructive pulmonary disease. *ProcAmThoracic Soc* 2008;5(9):878-83.
  46. Kohansal R, Martinez-Camblor P, Agusti A, et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009;180(1):3-10.
  47. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178(4):332-8.
  48. Geake JB, Dabscheck EJ, Wood-Baker R, et al. Indacaterol, a once-daily beta2-agonist, versus twice-daily beta2-agonists or placebo for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015;1:CD010139.
  49. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *Jama* 1994;272(19):1497-505.

50. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176(6):532-55.
51. Global Strategy for the Diagnosis MaPoCG. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 2017 [Available from: <http://goldcopd.org> accessed 26 April 2018.